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- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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- (75) Inventor/Applicant (*for US only*): MARTIN, Peter [DE/DE]; Buchensteige 4, 69251 Gaiberg (DE).
- Published:
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: METHOD FOR DISCRIMINATION OF METAPLASIAS FROM NEOPLASTIC OR PRENEOPLASTIC LESIONS

(57) Abstract: The present invention relates to a method for discrimination of p16^{INK4a} overexpressing metaplasias from neoplastic or preneoplastic p16^{INK4a} overexpressing lesions by determination of the level of high risk HPV encoded gene-products such as e.g. HPV E2 and/or HPV E7 molecules in biological samples in the course of cytological testing procedures. The method thus enables for reduction of false positive results in the p16^{INK4a} based detection of anogenital lesions in cytological testing procedures.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/574 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | MILDE-LANGOSCH KARIN ET AL: "Expression of cyclin-dependent kinase inhibitors p16MTS1, p21WAF1, and p27KIP1 in HPV-positive and HPV-negative cervical adenocarcinomas." VIRCHOWS ARCHIV, vol. 439, no. 1, July 2001 (2001-07), pages 55-61, XP001150380 ISSN: 0945-6317 the whole document ----- -/-- | 1-3,6-26 |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | RIETHDORF S ET AL: "Analysis of p16/MTS1, Ki67 and HPV 16/18 E6/E7 oncogene transcription in adenocarcinoma in situ and benign glandular lesions of the cervix uteri." VIRCHOWS ARCHIV, vol. 439, no. 3, September 2001 (2001-09), page 338, XP002238399 18th European Congress of Pathology; Berlin, Germany; September 08-13, 2001 ISSN: 0945-6317 abstract | 1-3,6-26 |
| X | ----- DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2002, WIEST TINA ET AL: "Involvement of intact HPV16 E6/E7 gene expression in head and neck cancers with unaltered p53 status and perturbed pRb cell cycle control." XP002238400 Database accession no. PREV200200210105 abstract & ONCOGENE, vol. 21, no. 10, 2002, pages 1510-1517, 28 February, 2002 ISSN: 0950-9232 | 1-3,6-26 |
| X | ----- WO 02 08764 A (MEDICAL RES COUNCIL ;DOORBAR JOHN (GB)) 31 January 2002 (2002-01-31) abstract page 3 - page 9 example 10 page 8, line 22 - page 9, line 27 page 13, line 22 - line 26 | 1,2,6-26 |
| X | ----- SANO T ET AL: "EXPRESSION STATUS OF P16 PROTEIN IS ASSOCIATED WITH HUMAN PAPILLOMAVIRUS ONCOGENIC POTENTIAL IN CERVICAL AND GENITAL LESIONS" AMERICAN JOURNAL OF PATHOLOGY, PHILADELPHIA, PA, US, vol. 153, no. 6, December 1998 (1998-12), pages 1741-1748, XP001023054 ISSN: 0002-9440 the whole document | 1,2,6-26 |
| P,X | ----- EP 1 217 377 A (BAYER AG) 26 June 2002 (2002-06-26) column 9, line 25 - column 10, line 21 ----- -/-- | 1,2,6-26 |

INTERNATIONAL SEARCH REPORT

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | <p>DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; March 2002 (2002-03), SDEK PATIMA ET AL: "[Influence of HPV16 on expression of Rb, p16 and cyclin D1 in oral epithelial cell]" XP002238401 Database accession no. NLM12475413 abstract & ZHONGHUA KOU QIANG YI XUE ZA ZHI = ZHONGHUA KOUQIANG YIXUE ZAZHI = CHINESE JOURNAL OF STOMATOLOGY. CHINA MAR 2002, vol. 37, no. 2, March 2002 (2002-03), pages 84-86, ISSN: 1002-0098</p> | |
| A | <p>----- WO 00 01845 A (VON KNEBEL DOEBERITZ MAGNUS) 13 January 2000 (2000-01-13) cited in the application the whole document</p> | |
| A | <p>----- KLAES RUEDIGER ET AL: "Overexpression of p16INK4a as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri." INTERNATIONAL JOURNAL OF CANCER, vol. 92, no. 2, 2001, pages 276-284, XP002225497 ISSN: 0020-7136 cited in the application the whole document</p> | |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/50096

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2 and 6-26 (all partially); 3 (complete)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2 and 6-26 (all partially); 3 (complete)

Method for discrimination of metaplasias from neoplastic or preneoplastic lesions based on assessing simultaneous presence of cells overexpressing p16-INK4a and cells expressing HPV E7 gene. Kit comprising probes for performing said methods.

2. claims: 1, 2, 4 and 6-26 (all partially)

Method for discrimination of metaplasias from neoplastic or preneoplastic lesions based on assessing simultaneous presence of cells overexpressing p16-INK4a and cells expressing HPV E2 gene. Kit comprising probes for performing said methods.

3. claims: 1, 2, 4 and 6-26 (all partially)

Method for discrimination of metaplasias from neoplastic or preneoplastic lesions based on assessing simultaneous presence of cells overexpressing p16-INK4a and cells expressing HPV E6 gene. Kit comprising probes for performing said methods.

4. claims: 1, 2, 5 and 6-26 (all partially)

Method for discrimination of metaplasias from neoplastic or preneoplastic lesions based on assessing simultaneous presence of cells overexpressing p16-INK4a and cells expressing HPV L1 gene. Kit comprising probes for performing said methods.

5. claims: 1, 2, 5 and 6-26 (all partially)

Method for discrimination of metaplasias from neoplastic or preneoplastic lesions based on assessing simultaneous presence of cells overexpressing p16-INK4a and cells expressing HPV L2 gene. Kit comprising probes for performing said methods.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50096

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
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